REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. Claims 7-9 are allowed. Claims 3-9, 11, 14 and 16 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 3-6 and 11 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants believe that this rejection is obviated by the amendment to the claims.

Claims 3 and 11 are now amended by adding the definition "at least 90% homologous to, but different from the amino acid sequence of SEQ ID NO:2" to the variant/protein. While there does not appear to be explicit support for at least 90% homologous" in the specification as filed, applicants believe that the specification as filed does provide implicit support for the definition "at least 90% homologous" at page 9, third paragraph to page 13, first paragraph.

To support applicants' position, a declaration executed by Dr. Haruki OKAMURA, one of the inventors, is attached hereto along with copies of references cited therein. Dr. Okamura states in the attached declaration:

> 10. The specification is silent about the specific homology of the above-identified variants to the protein with the amino acid

> sequence of SEQ ID NO:3. However, I and other co-inventors had in mind that such variants are those which are at least 90% homologous to but different from the protein with the amino acid sequence of SEQ ID NO:3, based on the previous publications which show the percentages of homology among interleukins (ILs) of animals, particularly, rodents such as mice and rats. Examples of such publications are listed in "16. References", i.e., references (a) to (f). (please see paragraph 10)

Please note that "SEQ ID NO:3 in the specification as filed was amended to "SEQ ID NO:2" with the preliminary amendment filed August 12, 1999. Therefore, "SEQ ID NO:3" in the declaration corresponds to "SEQ ID NO:2" of the claimed invention. Similarly, the nucleotide sequence of "SEQ ID NO:4" in the declaration corresponds to SEQ ID NO:3 of the presently claimed invention.

Applicants believe that the amendments made to claims 3 and 11 are not new matter and well define the metes and bounds of the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 3-6 remain rejected under 35 U.S.C. S112, first paragraph, because the examiner states that the specification does not reasonably provide enablement for "a sequence variant of

SEQ ID NO:2" in claim 3. This rejection is respectfully traversed.

In the attached declaration, Dr. OKAMURA further states:

> 6. I and other co-inventors of the present invention screened a protein which induces interferon-γ (IFN-γ) production by immunocompetent cells. As a result, I and other co-inventors first discovered a novel protein, i.e., interleukin 18 (IL-18), from mouse and then revealed its amino acid sequence and nucleotide sequence; an amino acid sequence of SEQ ID NO:3 and a nucleotide sequence of SEQ ID NO:4 in the original specification of the above-identified patent application (called "the specification", herein after), respectively.
>
> 7. At the time the invention was made, once the above information were available, then the skilled person in the art could have easily understood and engineered various variants of the protein with the amino acid sequence of SEQ ID NO:3, i.e., a variety of polypeptides which are homologous to the protein, where one or more amino acid in SEQ ID NO:3 are replaced with other amino acids, one or more amino acids are added to the amino acid sequence of SEQ ID NO:3, particularly, to the N- or C-terminal region in SEQ ID NO:3; and/or one or more amino acids are deleted from the amino acid sequence of SEQ ID NO:3, particularly, from the N- or C-terminal region of SEQ ID NO:3, without altering the inherent biological properties of the protein with the amino acid sequence of SEQ ID NO:3.

In view of the above, it is clear that one of skill in the art could easily obtain various variants of the amino acid sequence

of SEQ ID NO:3 (i.e., SEQ ID NO:2 of the presently claimed invention) once the amino acid sequence of SEQ ID NO:3 was available at the time the present invention was made.

To support applicants' arguments, attached to the Okamura declaration is a copy of J. D. Watson et al. "Recombinant DNA", second edition, SCIENTIFIC AMERICAN BOOKS, 1992, pp.191-211, 453-470. The examiner's attention is invited to page 193, left column; page 201, right and left columns; the paragraph bridging pages 204 and 206 of the publication. In particular, this reference discloses at page 466, right column:

> This experiment points out the power of recombinant DNA as a tool for the engineering of natural products. Changing the properties of a protein was all but impossible prior to the development of recombinant DNA techniques. Now it is not only possible, but easy. It is a routine exercise for protein engineers to generate hundreds of variants of a natural protein for testing. These changes can be educated guesses based on detailed knowledge of the structure of a protein; alternatively, changes can easily be made on a purely random basis. And, as we will see in the next section, a combination of structural information with random mutagenesis and a powerful selection for improved protein function can have dramatic results. (emphasis added)

Applicants wish to draw the examiner's attention to the fact that a variant of an interferon-gamma production inducing protein of claim 3 has the specified physicochemical properties of (1)

Molecular weight, (2) Isoelectric point, (3) Biological activity, (4) Partial amino acid sequence, (5) Purity and (6) Assay in addition to the amino acid sequence of "at least 90% homologous to, but different from the amino acid sequence of SEQ ID NO:2, while substantially having the above biological activity (3)".

It would be easy and routine for one skilled in the art to determine if a given protein can be "a variant of an interferon-gamma production inducing protein" of claim 3, because the specification provides all the guidance for determining the physicochemical properties as specified in (1) to (6) of claim 3 and the amino acid sequence of SEQ ID NO:2. Applicants therefore submit that the specification provides enablement for "a variant of an interferon-gamma production inducing protein" as defined in the amended claim 3. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 2, 11, 14 and 16 remain rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for any IL-18 or variants with properties listed in the claims. This rejection is respectfully traversed.

Rejected claims 1 and 2 are cancelled and rejected claims 11, 14 and 16 are amended in the same way as in claim 3. Applicants therefore believe that the specification reasonably

provides enablement for claims to variants having physicochemical properties of (1) to (6) and the amino acid sequence of "at least 90% homologous to, but different from the amino acid sequence of SEQ ID NO:2, while substantially having the above biological activity (3)".

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-6, 11, 14 and 16 remain further rejected under 35 U.S.C. §112, first paragraph, for lack of written description. Applicants believe that this rejection is made moot by the cancellation of claims 1 and 2 and the amendment to claims 6, 11, 14 and 16.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-3, 5, 6, 11, and 14-17 remain rejected under 35 USC 102(b) as being anticipated by Nakamura et al. (Infect. Immun. 61: 64-70, 1993). This rejection is respectfully traversed.

Attached hereto is a copy of another declaration of Dr. Haruki OKAMURA, which was filed with the European Patent Office in connection with European Patent No.0712931 of the same applicant. Dr. OKAMURA, who signed the declaration and who is

one of the inventors of the present application, is also one of the authors of the cited and applied Nakamura et al. reference.

Dr. OKAMURA states in his declaration that:

> 11. Also, based on our finding that the apparent molecular weight of the active form of NKSF/interleukin-12 (IL-12); its IFN-γ inducibility; and the synergy with interleukin-2 (IL-2), anti-CD3 MAb, or the dynamics against mitogenic lectin were all similar to those of the factor of D2 (see page 69 left column, lines 25 to 28), we speculated that the factor of D2 could possibly be NKSF/interleukin-12 (IL-12) similarly as the factor of D1.

It should be noted that the document D2 referred in the declaration is the presently cited and applied prior art reference of Nakamura et al., Infect. Immun. 61:64-70, 1993). Therefore, it is clear that Dr. OKAMURA, one of the authors of the cited Nakamura et al. reference, *per se*, did not consider that the factor disclosed in Nakamura et al. is the same protein as claimed in the present invention. Accordingly, Nakamura does not anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their

allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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